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Abstract: Clinicians frequently monitor serum C-reactive protein (CRP) levels during therapy for diabetic foot infections (DFIs), but evidence supporting this is unclear. Using a database from prospective controlled DFI trials, with fixed duration of antibiotic therapy, we correlated the CRP levels at study enrolment and at end of therapy (EOT). Among 159 DFI episodes, 93 involved the bone and 66 the soft tissues. Overall, treatment cured 122 infections (77%), while 37 episodes (23%) recurred after a median of 53 days. The median CRP in the groups with cure versus failure differed minimally at enrolment (median 67 vs. 81 mg/L) or EOT (7 vs. 10 mg/L). Similarly, there was negligible difference in the percentage of CRP levels that normalized at EOT (39% vs. 35%). In our prospective cohorts, a blunt iterative monitoring of CRP during DFI treatment, without correlation with clinical findings, failed to predict treatment failures.

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Is Routine Measurement of the Serum C-Reactive Protein Level Helpful During Antibiotic Therapy for Diabetic Foot Infection?

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ABSTRACT

Clinicians frequently monitor serum C-reactive protein (CRP) levels during the therapy of diabetic foot infections (DFI), but evidence supporting this is unclear. Using a database from prospective-controlled DFI trials, with fixed duration of antibiotic therapy, we correlated the CRP levels at study enrollment and at end of therapy (EOT). Among 159 DFI episodes, 93 involved the bone and 66 the soft tissues. Overall, treatment cured 122 infections (77%), while 37 episodes (23%) recurred after a median of 53 days. The median CRP in the groups with cure versus recurrent infection differed minimally at enrollment (median 67 mg/L vs. 81 mg/L) or EOT (7 mg/L vs. 10 mg/L). Similarly, there was negligible difference in the percentage of CRP levels that normalized at EOT (39% vs. 35%). In our prospective cohorts, a blunt iterative monitoring of CRP during DFI treatment, without correlation with clinical findings, failed to predict treatment failures.

INTRODUCTION

Clinicians frequently monitor serum C-reactive protein (CRP) levels[1,2] during the treatment of diabetic foot infections (DFI). This is usually in hopes of assessing the evolution of infection, attempting to provide a prognosis, or being forewarned of problems. Unfortunately, failure of CRP levels to fall may trigger unnecessary diagnostic studies (imaging, angiology procedures, additional cultures) or therapeutic interventions (altering antibiotic therapy, surgical or adjunctive treatments), even in absence of clinical indications. Of particular concern in this era of growing antibiotic resistance is the unnecessary broadening or prolongation of the antibiotic regimen based more on CRP levels[3] than clinical findings[4]. Evidence for the value of monitoring CRP in DFI patients remains unclear, especially since the CRP peak almost always lags behind the clinical evolution by about two days[1,5]. While some scientific literature supports using the quantitative serum CRP level in diagnosing the presence or severity of a DFI[1,4-7], infectious diseases experts generally emphasize that no therapeutic decision should depend solely on this laboratory result[8,9]. We undertook this study to provide more information based on the utility of routine serum CRP controlling during DFI therapy. In contrast we not address the role of the serum CRP in the diagnosis of DFI, including for the diagnosis DFO, for which a broader literature is available[8].

METHODS AND STUDY AIMS

Setting

At the Geneva University Hospitals, we performed two prospective-comparative trials, randomizing patients with DFIs to fixed durations of antibiotic therapy after (surgical) debridement (Ethical Committee BASEC 2016-01008). We assigned the duration of antibiotic therapy to either a short arm (10 days for soft tissue infections; 3 weeks for diabetic foot osteomyelitis [DFO]) and a long arm (20 days for soft tissue DFIs and 6 weeks for DFO); without crossovers throughout the trials.

Processing of the serum CRP

This database we assembled from these prospective studies allowed us to assess the predictive role of obtaining iterative serum CRP samples (or their dynamic change) on the likelihood of clinical treatment failure. The study treatment period included the following visits, whether as an inpatient or outpatient: Enrollment (Day 1); Day 10 (± 2 days); Day 20 (± 2 days); Day 42 (only if still receiving antibiotic therapy). The test-of-cure (TOC) visit occurred at 60 days (± 10 days) after the end of treatment (EOT). The CRP values were measured at enrollment and at the EOT, sometimes during each visit and sometimes between the visits at the discretion of the treating clinicians. According to the protocol of the randomized trials, which was based on standard advice for daily practice, CRP measurements were not required if all aspects of the patient's infection were stable or improving. We processed all serum CRP samples in our laboratory. A CRP-test cost 10 Swiss Francs (10 US $) and a value <10 mg/L was within the laboratory norms.

Statistical analyses

The primary outcome for this study was remission of DFI at the EOT visit, which we correlated with the serum CRP levels at study enrolment and at the TOC visit. We assessed whether or not baseline and EOT-CRP levels can be used to predict future treatment failure. For group comparisons we used the Pearson-χ^2, the Wilcoxon-ranksum, or the t-test, as appropiate. As this study was a side study, we did not determine any formal sample size requirement, as, moreover, the number of CRP samples collected was greater than the number of DFI episodes of the randomized studies. We used STATA™ software (15.0; College Station, Texas, USA) and assigned *P*-values <0.05 (two-tailed) as significant.

RESULTS

Study population

We enrolled 159 DFI episodes in the two trials: 93 DFO and 66 the soft tissue infections. Among the 159 episodes, 80 were treated with a short duration of antibiotics, and 79 a long duration. Overall, 122 episodes (77%) were clinically cured and 37 (23%) were failures, after a median of 53 days post-treatment. When stratified, the overall remission was 84% in the DFO group (44 episodes) with a short arm versus 73% in the DFO group with the long antibiotic arm (49 episodes). Regarding the 66 soft tissue DFIs, the cure incidences were 77% and 71%, respectively. All patients had CRP sampling, wound care, off-loading; and angioplasty in 21 cases. The minimal follow-up duration was 2 months after EOT, but the real active median follow-up time was 1 year. The most frequent pathogen was *Staphylococcus aureus* in 65 episodes (41%).

Association of clinical outcome with serum CRP levels

Although the CRP levels in the failed episodes were very slightly higher at both enrollment and at the EOT (absolute differences of 8-14 mg/L and 3-4 mg/L, respectively), the median CRP values at both time points (enrolment and EOT) were not statistically different (Table 1). Similarly, the same proportion patients of achieved normalization of their CRP values (i.e. drop to less than 10 mg/L) at the EOT (39% vs. 35%, Table 1). Equally, the relative drop (ratio of final CRP values divided by the admission level) was the same (median drop of 67% vs. 63%, Table 1). Table 1 compares the serum CRP levels at enrollment and EOT. Figure 1 summarizes the results graphically.

DISCUSSION

Using data from two randomized trials with fixed antibiotic therapies for DFIs, we found no association between the initial (enrollment) and final (EOT) serum CRP samples values and treatment failure. The variance of the results was high, implying a very large distribution of various CRP levels in the different strata (Figure 1). This finding was true for all strata: median values at enrollment and at EOT; the number of CRP values that normalized (<10 mg/L); or, the relative decrease in CRP values during therapy for DFI. These findings cast doubt on the widely-held view that following levels of CRP during therapy of DFIs helps predict the clinical outcome. In reality, measuring the CRP probably adds little or nothing to careful clinical assessment.

There are only few prospective studies examining the performance of CRP for the follow-up of DFOs. Michail et al. sampled various serum inflammatory markers in 61 patients with DFO after 1 week, 3 weeks, and 3 months of treatment[1] and found that all values declined after initiation of antibiotic therapy. Specifically, the CRP values returned to near-normal levels at Day 21, but their results did not clarify if there was any clinical benefit to routinely monitoring the CRP, or what that added to just careful clinical evaluation[1]. Similarly, Van Asten et al. measured CRP levels (along with other markers) in 35 patients with an infected diabetic foot ulcer at baseline, and after 3 and 6 weeks of antibiotic therapy[2]. They found that almost all values decreased in patients with a good outcome, but they provided no comparative analysis on the CRP values[2].

In the elderly population, in which DFIs are most common, the serum CRP levels are dynamic and influenced by many co-morbidities such as gout[10,11], cancer[10], rheumatic diseases[10], thrombosis[9], obesity[9-11], statins[11], hematoma[12], ischemia[11], dialysis[7], cirrhosis[13], or the postoperative state[5]. Also, the presence of diabetes itself may cause a slight elevation of CRP level[11]. Finally, CRP peak levels generally lag 2-3 days behind the causative events, making a timely interpretation impracticable[5,13].

The results of studies of routine serial serum CRP levels are equally reported in other fields of orthopedic surgery. Dupont et al monitored arthroplasties and concluded that local wound discharge, body temperature and pain are more informative indicators of

postoperative infection than the evolution of the CRP[14]. Similarly, Bejon et al evaluated 260 infected arthroplasties with 3732 CRPs and found that the CRP was a poor predictor of outcome[15]. Their area under the ROC curves for the CRP levels predicting a good outcome ranged from 0.55 to 0.65, thus only slightly better than a coin toss[15].

Our study has two main strengths: the large population makes it statistically well-powered and it is based on a prospective database. It has also important limitations.
First, the CRP samples were collected as a sub-study. A randomized-controlled trial designed to assess the routine use of CRP as its primary objective would gather additional data, such as discontinuing antibiotic therapy after the normalization of the CRP. While such a trial would be innovative, it is not realistic. For DFI the total duration of antibiotic therapy is determined by expert opinion[8] (often codified in guidelines) based on few data[9], and not on a single laboratory parameter[8,9].
Second, we are unable to assess which additional clinical examinations were triggered by an unexpectedly elevated CRP level. Although we have a comprehensive database documenting regular medical and nursing care and validated case report forms, we cannot determine if the motivation of the individual clinician for ordering a specific additional examination was related to noting an elevated CRP level.
Third, we determined only the standard laboratory test for serum CRP. Thus, our findings may not apply to other inflammatory markers, such as pro-calcitonin[2,4,5], erythrocyte sedimentation rate[2,4,6], interleukins 2, 6 or 8[2,4], serum leukocyte counts[4], tumor necrosis factors[2,4], monocyte chemotactic protein[4], macro-phage inflammatory

protein-1 alpha[4], neutrophil to lymphocyte ratios[6], procollagen type 1 N propeptides[2,4], or high-resolution CRPs. However, these other markers are seldomly used in daily clinical practice and all are more expensive than the standard CRP. Likewise, the potential heterogeneity of the factors (such as interventional procedure, additional comorbidity or different treatments) and the fact that CRP values were not compared with other infectious parameters might impair the universality of the result. We need other studies to identify the accuracy of different biomarkers in DFI therapy.

In conclusion, in our prospectively-collected database, collecting routine CRP samples, at different time points during ongoing therapy for DFI, failed to predict the clinical outcomes. Based on these results, and our review of the available literature, we recommend abandoning ordering such routine CRP level. Ordering these clinically unhelpful samples wastes money, leads to unnecessary discomfort and time-expenditure associated with phlebotomies for patients and nurses, and often leads to further unneeded and excessive diagnostic evaluations.

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Conflict of Interest and funding

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Author contributions

T.T.P., K.G., B.K., P.S., F.J., I.U.: design, database

T.T.P., K.G., B.K., F.J., I.U.: study conduct, database, supervision, corrections

I.U., B.A.L.: analyses, control, writing

O.W.: analysis, writing

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Figure legend

Figure 1: Median serum C-reactive protein values at enrollment and at end of treatment; stratified between non-infectious complications and infections.

The bars in the middle of the columns represent the 95% confidence intervals. Of note, these intervals are very wide and many patients (35-39%) yielded baseline CRP values between 1-10 mg/L (normal range of our laboratory).

Table 1. Serum C-reactive protein levels in two comparisons: cure vs. infection recurrence; clinical remission vs non-infectious failures

n = 159	**Cure of infection** n = 122	**Recurrence infection** n = 37	*p*-value *
Median CRP level at study enrolment	67 mg/L (range, 1-127 mg/L)	81 mg/L (range, 1-324 mg/L)	ns
- *mean CRP with standard deviation*	- *83 mg/L* (± *72 mg/L*)	- *108 mg/L* (± *94 mg/L*)	ns
Median CRP level at end of therapy	7 mg/L (range, 1-127 mg/L)	10 mg/L (range, 2-134 mg/L)	ns
- *mean CRP with standard deviation*	- *14 mg/L* (± *20 mg/L*)	- *25 mg/L* (± *33 mg/L*)	ns
Median CRP for bone infection (start)	63 mg/L (range, 1-306 mg/L)	99 mg/L (range, 2-322 mg/L)	ns
Median CRP for bone infection (end)	6 mg/L (range, 1-72 mg/L)	9 mg/L (range, 4-79 mg/L)	ns
Median CRP for soft tissue infection (start)	67 mg/L (range, 1-334 mg/L)	71 mg/L (range, 1-324 mg/L)	ns
Median CRP for soft tissue infection (end)	9 mg/L (range, 1-127 mg/L)	14 mg/L (range, 2-134 mg/L)	ns
Median drop CRP (ratio end/admission values)	51%	79%	ns
Normalized CRP at the end (< 10 mg/L)	47 (39%)	13 (35%)	ns

n = 159	**Clinical remission** n = 103	**Non-infectious failure** n = 56	*p*-value *
Median CRP level at enrolment	68 mg/L (range, 1-334 mg/L)	76 mg/L (range, 1-324 mg/L)	ns
- *mean CRP with standard deviation*	- *90 mg/L* (± *75 mg/L*)	- *87 mg/L* (± *83 mg/L*)	ns
Median CRP level at end of therapy	7 mg/L (range, 1-72 mg/L)	11 mg/L (range, 2-134 mg/L)	ns
- *mean CRP with standard deviation*	- *12 mg/L* (± *15 mg/L*)	- *25 mg/L* (± *33 mg/L*)	ns
Median drop CRP (ratio end/admission values)	67%	63%	ns
Normalized CRP at the end (< 10 mg/L)	41 (39%)	19 (34%)	ns

* Pearson-χ^2 or Wilcoxon-ranksum-tests. ns = not significant (*p*-value >0.05).